REMARKS

I. On page 3 of the Office Action, claims 1-3, 27, 28, 30, 31 and 38 were rejected under 35 U.S.C. 103(a) over WO99/26480 of Leboulch et al. in view of U.S. Pat. No. 6,555,107.

According to the Examiner, Leboulch et al. enably teach a method for treating diabetic retinopathy, which can result in corneal, retinal and iris neovascularization, using, for example, a retroviral vector carrying an endostatin gene sequence which is administered in a manner that allows the vector access to the target cells, such as the retina, page 3, second full paragraph of the Office Action.

In the third full paragraph on page 3 of the Office Action, the Examiner noted that Leboulch et al. do not teach lentiviral vectors and the particular lentivirus of interest, bovine immunodeficiency virus (BIV). The Examiner thus turned to the '107 patent, which makes only passing mention of BIV as the '107 patent focuses on FIV. Nevertheless, to support the rejection, the '107 patent was asserted to teach that BIV is a preferred vector for transfecting non-dividing cells of the nervous system.

The rejection is traversed for the following reasons.

The use of endostatin according to the claimed invention is not obvious

The instant invention relates to the use of an endostatin, which at the time of the invention, was <u>not</u> viewed as providing a predictable use for reducing ocular neovascularization because endostatin, in general, had been found <u>not</u> to have an overall biological effect in attempts to beneficially inhibit neovascularization, for example, in various types of cancers.

The prior art must enable an invention

According to In re Kumar, 418 F.3d 1361 (Fed. Cir. 2005),

> "...to render an invention unpatentable for obviousness, the prior art must enable a person of ordinary skill to make and use the invention. ...rebuttal may take the form of evidence that the prior art does not enable the claimed subject matter."

Applicants have maintained, and have provided evidence in the record that the Leboulch et al. reference is not enabled.

References can establish non-enablement and inoperability of prior art

A holding of In re Donahue, 766 F.2d 531 (Fed. Cir. 1985) directs that secondary references can be used to establish that the teachings of prior art were possessed by the public, that is, the teachings of the prior art are enabled. Thus, in the Donahue case, two references were relied on to support an anticipation rejection over a third reference, the first two references teaching how to make starting materials that can be used in the practice of the teachings of the third reference.

Therefore, it follows that one or more references can be relied on to prove whether prior art on which a rejection relies is not enabled or is inoperable.

References are to be fairly viewed for all that is taught therein

In the case of In re Langer, 465 F.2d 896 (CCPA 1972), the Examiner and the Board of Appeals rejected the Langer application as obvious over a reference teaching one species among a long list of species. The Langer process required a sterically hindered amine. A reference

taught a list of amines, all but one of which were unhindered. The rejection was based on that single unhindered amine species. The US Court of Customs and Patent Appeals held that,

> "...disclosures in a reference must be evaluated for what they fairly teach one of ordinary skill in the art. ...when "all of the disclosures in a reference" are considered, the overall suggestion to emerge from the prior art reference may be contrary to that which might appear from an isolated portion of the reference."

Similarly, in the Shaub case, In re Shaub, 950 F.2d 732 (Fed. Cir. 1991), claims to a method not requiring emulsifiers were rejected over a reference (Grolitsch) that teaches flowable fat powders and Grolitsch teaches the powders may be used in combination with an emulsifier. The Federal circuit held that,

> "The board clearly erred in concluding that, because Grolitsch states that it is "possible" to add emulsifiers to fat powders, the reference also meets the claim limitation requiring an absence of emulsifiers. Such a conclusion is not based on a fair reading of the reference as a whole. Grolitsch adds an emulsifier in four of its five examples. No emulsifier is required in the fifth example because the milk fat utilized in that example exists naturally as an oil-in-water emulsion. The mere statement that an emulsifier may be used, when all of the examples describe fat particles that form an emulsion, cannot be construed as an affirmative statement that emulsifiers should not be present." In re Shaub, 950 F.2d 732 (Fed. Cir. 1991).

Therefore, a fair reading of a document describing experimentation directed to addressing a question should consider the overall focus of the document. It is improper to extract an excerpt that is inconsistent with the general nature and conclusions of the document.

WO99/26480, which has not been patented, is not enabled on the use of endostatin

Thus, it follows that a publication that describes actual experiments must be considered for what that experimentation revealed. As is known, in publications, the standard practice is to provide an introduction or background that lays the groundwork for the experimentation conducted. The introduction selectively briefs what of relevance to the experiments to be

conducted has been reported in the literature. There is no representation that such citation of a publication in the introduction establishes the truth of any publication named in the introduction. Thus, to rely only on passages from the introduction of a publication is not a fair reading of the publication as a whole.

Applicants provided in the record evidence in the form of publications by third parties demonstrating that the Leboulch document is not enabled. Numerous attempts to replicate the teachings of the Leboulch reference, including attempts by Leboulch, demonstrated that the teachings of WO99/26480 are not enabled. On several occasions in the record, passages from the introductions of those publications were relied on for a conclusion of enablement on the use of endostatin.

For example, inability of an independent laboratory to replicate the results of WO99/26480 is documented in Jouanneau et al., J Neuro-Oncol 51:11-18, 2001, of record, published in January of 2001 and cited in the Guo Declaration of 26 March 2007. That publication concluded there is a lack of antitumor activity by endostatin in a human neuroblastoma model.

A fair reading of Jouanneau et al. would not place more value on the references from the Folkman lab mentioned in the introduction than on the results of the Jouanneau et al. research. Mention of the Folkman work provided no more than a reason for the authors to conduct their experiments attempting to replicate the work of Folkman. The introduction is not an affirmation or confirmation of the truth of the science advanced in publications from the Folkman lab. Thus, a fair reading of Joaunneau et al. would consider the materials, methods, results and conclusions based on the data and results. That fair reading of Jouanneau et al. is that endostatin did not have an antiangiogenic effect on cancer cells.

Applicants have established on the record in the form of publications and Declarations that Leboulch et al. is not enabled for all that is taught therein. With regard to cancer, attempts to replicate Leboulch et al., as well as the foundational research of the Folkman lab, have failed.

Thus, there is no basis to conclude that any one embodiment disclosed in Leboulch et al. is enabled and can be relied on to ground a rejection.

There is no reasonable expectation of success or no basis to expect predictable results

As advanced in Boehringer Ingelheim v. Schering-Plough, 320 F.3d 1339 (Fed. Cir. 2003),

> "...there can be little better evidence negating an expectation of success than actual reports of failure."

Evidence of record demonstrating endostatin was unsuccessful in reversing the growth of cancer by antiangiogenesis would lead to the conclusion that an artisan would not have a reasonable expectation of success in practicing the teachings of Leboulch et al., and for that matter, the teachings of Folkman in general.

The uniform failures to independently replicate the research of the Folkman lab and the teachings of Leboulch et al. yield one conclusion, the Leboulch et al. reference does not provide an artisan with a reasonable expectation of successfully using endostatin. It follows that the repeated lack of success in use of endostatin as an antiangiogenic drug leads to the only predictable result, that endostatin will not have any antiangiogenic activity. There is no legal basis, based on the repeated failures, to conclude the contrary.

Teaching away dissolves an asserted motivation to combine

In re Gurley (27 F.3d 551 (Fed. Cir. 1994)) held,

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would led in a direction divergent from the path that was taken

> by the applicant. ...in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant... ...known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness... ...reference teaches away if it leaves the impression that the product would not have the property sought by the applicant." (underlining added)

The record contains evidence that endostatin uniformly did not have an antiangiogenic activity in the preclinical or clinical trial indications tested. Those references clearly teach away from practicing Leboulch et al. and teaching away from combining Leboulch et al. and the '107 patent, as the '107 patent is relied on merely to provide a vector means, and does not cure the lack of reproducibility as to endostatin.

Thus, a prima facie case of obviousness has not been made. Moreover, as noted in the record, there are facts and evidence of secondary indicia that would overcome any asserted case of obviousness. Accordingly, withdrawal of the rejection is in order.

II. On page 4 of the Office Action, claims 1, 32 and 38-41 were rejected under 35 U.S.C. 103(a) over WO99/26480 of Leboulch et al. in view of U.S. Pat. No. 6,555,107 and further in view of U.S. Pat. No. 6,106,826.

According to the Examiner, Leboulch et al. teach a method for treating diabetic retinopathy, which can result in corneal, retinal and iris neovascularization, using a retroviral vector carrying an endostatin sequence, page 4, lines 13-19 of the Office Action. In the first full paragraph on page 5 of the Office Action, the Examiner indicated that Leboulch et al. do not specifically teach the bovine lentivirus, which can be administered, for example, intraocularly, subretinally or intravitreally. The Examiner then turned to the '107 patent for an asserted teaching of BIV vectors and then the '826 patent for the modes of administration to the eye.

The rejection is traversed for the following reasons.

The arguments and discussion hereinabove and of record are herein incorporated by reference in entirety as to the primary and secondary references.

As clearly provided hereinabove, Leboulch et al. and the '107 patent both are deficient as to teaching or suggesting the claimed subject matter. The Leboulch et al. document does not teach or suggest to one skilled in the art at the time of the invention a predictable use of endostatin. The '107 patent does not teach or suggest whether BIV can be used to make a vector, and how to achieve that goal. Thus, alone or together, Leboulch et al. and the '107 patent are insufficient to ground an obviousness rejection.

The '826 patent is relied on to teach particular modes of drug administration. The '826 patent does not relate to endostatin or to lentivirus. Hence, the '826 patent does not cure the fatal deficiencies of Leboulch et al. and of the '107 patent, taken alone or together.

Clearly a prima facie case of obviousness has not been made. Even if, arguendo, a prima facie case were made, the secondary considerations associated with the claimed subject matter summarized in the record, herein incorporated by reference in entirety, overcome any such hypothetical case of obviousness.

Accordingly, withdrawal of the rejection is requested respectfully.

III. On page 6 of the Office Action, claims 51-55 were rejected under 35 U.S.C. 103(a) over WO99/26480 of Leboulch et al. in view of U.S. Pat. No. 6,555,107 and further in view of Keshet et al. and Otani et al.

The Examiner relied on Keshet et al., a prospective piece presenting the opinions of the two authors, for the proposition that endostatin has antiangiogenic activity.

Otani et al. was relied on to teach the assertion of a possible role of VEGF in angiogenesis.

The rejection is traversed for the following reasons.

The discussion above as to Leboulch et al. and the '107 patent, and in the record are incorporated herein by reference in entirety.

Keshet et al. does no more than summarize the research of the Folkman lab. As noted in the left column on page 1500, Keshet et al. summarized the early work of Folkman, which now has been found not replicable as evidenced, in part, by the publications and Declarations of record. In the paragraph bridging the columns on page 1500, Keshet et al. speculated on how endostatin could be used in therapy and what avenues may need to be considered given the then existing limitations.

It can be seen that the Keshet al. reference is no more than cumulative to Leboulch et al. and does not cure the deficiencies of Leboulch et al.

Clearly a prima facie case of obviousness has not been made. Even if, arguendo, a prima facie case were made, the secondary considerations associated with the claimed subject matter summarized in the record, herein incorporated by reference in entirety, overcome any such hypothetical case of obviousness.

Accordingly, withdrawal of the rejection is requested respectfully.

IV. On page 8 of the Office Action, claims 51 and 56-58 were rejected under 35 U.S.C. 103(a) over WO99/26480 of Leboulch et al. in view of U.S. Pat. No. 6,555,107 and further in view of Keshet et al. and Otani et al. and the Brandt patent.

The rejection is traversed for the following reasons.

The discussion above as to the references relied on and in the record are incorporated herein by reference in entirety.

Clearly a prima facie case of obviousness has not been made. Even if, arguendo, a prima facie case were made, the secondary considerations associated with the claimed subject matter summarized in the record, herein incorporated by reference in entirety, overcome any such hypothetical case of obviousness.

Accordingly, withdrawal of the rejection is requested respectfully.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance and early indication of such is requested respectfully. Reexamination, reconsideration, withdrawal of the rejections and early indication of allowance are solicited earnestly.

Respectfully submitted,

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